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(71) Applicants *(for all designated States except US)*: NOBEL BIOCARE AB (publ) [SE/SE]; Box 5190, S-402 26 Göteborg (SE). GS DEVELOPMENT AB [SE/SE]; Jägershillgatan 15, S-213 75 Malmö (SE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: LARSSON, Cecilia [SE/SE]; Brödragatan 26, S-412 74 Göteborg (SE). LJUSBERG-WAHREN, Helena [SE/SE]; Gränsvägen 18B, S-236 33 Höllviken (SE).

(74) Agent: OLSSON, Gunnar; Nobel Biocare AB (publ), Box 5190, S-402 26 Göteborg (SE).

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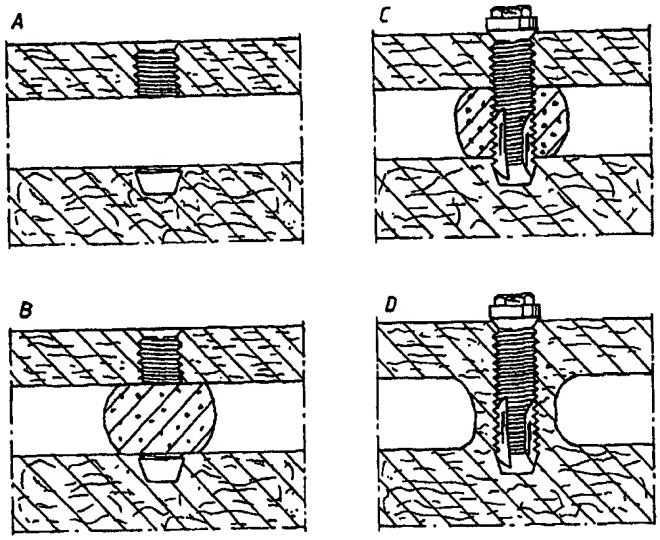

(57) Abstract

The invention relates to a preparation for restoring bone in the body of humans or animals in connection with an existing structure, a bone implant or some other prosthetic construction, as well as a method for restoring bone. The bone restoring preparation consists of an easily handleable and controllable preparation (composition) of resorbable calcium phosphate granules and a carrier of a biopolymer or lipid type. The preparation is intended to be applied in the position where the bone needs to be replaced, reinforced or built up, especially in connection with a bone implant or some other prosthetic construction where there is a lack of sufficient bone volume, or where the quality of the bone is too poor to allow a load-carrying function, for example permanent fixing of an implant.

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Material for bone reconstruction

The invention relates to a preparation for restoring bone in the body of humans or animals in connection with an existing structure, a bone implant or some other prosthetic construction, as well as a method for restoring bone. The bone restoring preparation is an easily handleable and controllable preparation (composition) adapted to be applied in the position where the bone need be replaced, reinforced or built up, particularly in connection with a bone implant or some other prosthetic construction where the bone volume is insufficient, or where the quality of the bone is too poor to allow a load carrying function, for example permanent fixing of an implant.

By bone implant is in this context meant, for instance, a helical, bone-anchored implant of titanium or a titanium alloy, a so-called fixture, but also comprises other types of implant intended to be installed in bone tissue including bone from humans, especially particulated bone, but also in combination with large cortical and/or spongious bone transplants.

Background

Different types of bone grafts have been used more or less successfully to replace lost bone tissue and improve healing of bone defects for the purpose of restoring the function with and without fixed implants. In autogenous transplantation, usually from the patient's own iliac crest, it is among other things the amount of bone and the degree of resorption that affect the result of the treatment. Autologous bone grafting usually requires more than one operation to achieve a satisfactory result and causes considerable postoperative pain to the patient. In homologous bone grafting, use is made of, for instance,

demineralised bone matrix from a so-called bone bank. Tissues and structure which have been lost owing to diseases or injuries can today to some extent be replaced by prosthetic constructions which are mechanically fixed to the skeleton. Artificial hips, artificial knee-joints and dental implants are examples of how lost tissue, structure and function can be replaced by this type of construction.

Replacing lost teeth by placing dental implants in the skeleton (jaws) has a high frequency of success provided that there is a sufficient amount of bone of good quality in the close vicinity of and round the implant. After an individually adapted time of healing (3 months - 2 years), prosthetic constructions can in most cases be secured to the osseointegrated implants. Some patients have, owing to many years of lack of teeth, obtained impaired conditions than others for obtaining treatment by means of bone-secured implants. It is mainly areas in the upper jaw that have suffered most from bone destruction when the teeth are lost owing to anatomical conditions, but also areas far back in the lower jaw can have a poor quality for implant treatment.

General states of ill-health such as osteoporosis and local defects and lack of bone owing to, for instance, acute injuries, congential defects, chronical infections or local biological processes such as cysts and tumours in the jaws in most cases affect and may even make treatment with implants impossible if bone is not added or replaced in some way to increase the amount of bone locally round the implants and, thus, the initial stability.

For patients who have been treated with implants and bone replacement materials, it is important to reduce the time of osseointegration and guarantee a higher frequency of

success after installation than is possible today. For decades, experiments have been made to replace bone with organic and synthetic materials from different sources, see review, Smiler et al (1992)[1] including resorbable and non-resorbable polymers, bioactive glass, calcium phosphate compounds, calcium carbonates and naturally occurring materials such as cow bone and coral. Transplanting bone from the patient, so-called autograft, is as described above an alternative, but a relatively extensive operation which requires specialist competence, hospital treatment, an extended healing period for the transplant of at least six months and additional inconvenience and pain to the patient. Demineralised freeze-dried bone from a so-called bone bank and spongious bone with mineral from cow bone also result in an extended period of healing, a risk of immunological reactions and infectious states, but also a risk in other aspects including the frequency of success.

There is thus a great need, both with specialists and non-specialists, for being able to apply an easily accessible safe preparation for restoring bone in connection with implant treatment of patients having an insufficient volume of bone and/or too poor bone quality.

An object of the invention is to provide a preparation for restoring bone, which enables implant treatment for patients in various situations especially in areas that otherwise cannot be treated and/or have a poorer prognosis.

Calcium phosphate compounds are so-called biocompatible materials, i.e. materials which are mildly reactive with the environment, i.e. promote repair and integration of, for instance, an implant, see Jarcho[2] and Lemons[3]. The commonest form of calcium phosphate compound that is used to stimulate ossification is hydroxylapatite (HA),

$Ca_{10}(PO_4)_6(OH)_2$, but also other compounds containing calcium and phosphate ions exist and resemble the inorganic ingredients in skeleton and enamel, see Daculsi et al (1997)[4]. Stoichiometric HA, $Ca_{10}(PO_4)_6(OH)_2$, with a Ca:P ratio of 1.67 is seldom found *in vivo*. Calcium is to some extent replaced by other ions, such as magnesium, sodium, aluminium, strontium, carbonate, fluorine and chlorine, depending on, inter alia, age, food, sex etc. of the individual. HA may be present in a ceramic and in a non-ceramic form where the degree of crystallinity may vary depending on the temperature at which the calcium phosphate compound is prepared, Ricci et al (1992)[5].

Calcium phosphate compounds such as hydroxylapatite are commercially available and produced by many companies; Impladent Ltd, Holliswood, New York, USA, Asahi Optical Co, Ltd, Tokyo, Japan, Interpore Int. and Irvine, California, USA. The materials are produced with different properties such as the size of the granules/particles, the degree of resorbability and the chemical composition.

The particles/granules being resorbed do so slowly after application in the bone tissue. It is considered that from the beginning the granules physically take up room in the defect and thus allow an accelerated integrating process compared with an empty defect. While the new bone is forming, mineralising and remodelling, the granules are resorbed slowly for about 3-8 months depending on patient-related factors including the size of the defect and the age of the patient.

There are experimental studies, Hürzeler et al (1995)[6] and Wetzel et al (1995)[7] and clinical studies, Smiler et al (1992)[1], Ricci et al (1992)[5], Judy (1986)[8], Wagner (1989)[9], and Corsair (1990)[10], which demonstrate a certain effect of resorbable granules (Osteogen®) mixed with, for instance, patient blood, common salt or above all in

combination with demineralised freeze-dried bone. The possibility of making a filling in sinus maxillaris (sinus of the upper jaw) to increase the possibilities of implant fixing in dogs shows that resorbable HA granules function well and the product is suitable for use to stimulate bone formation round dental implants, Wetzel et al (1995)[7]. However, the granules are mixed with patient blood or common salt, which makes the product difficult to handle. A great drawback of this form/technique of preparation is that it is technically difficult to pass the mass of granules to the defect/cavity area. Having applied the granules, there is a great risk that blood and other body fluids from the area of the wound dilute and transport the material away from the area of application. A further drawback of uncontrolled mixing of, for instance, common salt or the patient's blood is that the risk of contamination of the preparation increases.

Alpher et al (1989)[11] have tried to solve the handling problems. However this reference shows that a mouldable hydroxylapatite preparation based on phospholipids and stearic acid generally does not stimulate the formation of new bone or bone growth, but instead the results indicate a reduction of the bone formation.

Lipids can be divided into different classes. Triglycerides are the most frequent class of lipids and are an important depot of energy in cells. Triglycerides are either built up or decomposed in the body by the intermediary of diglycerides from or into monoglycerides and fatty acids. The body also contains different types of membrane lipids, for example phosphatidyl choline, phosphatidyl ethanolamine, sphingomyelin, cholesterol, mono- and digalactosyldiacylglycerol.

Phospholipids can be prepared fully synthetically but also be cleaned of biological raw materials such as

plants or animals. Examples of raw materials are egg yolk, vegetable oils such as soybean oil, rapeseed oil.

It is also preferred for the preparation to contain antioxidants selected according to known principles or naturally occurring. An example of an advantageous antioxidant in this case can be tocopherol. Liposomes consist of a spherical shell of amphiphilic lipids containing an aqueous phase. The potential of the lipid vesicles as carrier of drugs has been studied and described in a number of articles. Huang et al[12] have suggested that negatively charged liposomes can affect the mineralising process of newly formed bone. This concept was tested in a defect model in miniature swine, however, without any effect. Bone formation between uncoated and liposome-coated calcium phosphate compounds was compared and the uncoated calcium phosphate compounds were surrounded by more bone and riper bone than the liposome-coated ones. In an experimental study by Raggio et al (1986)[13], the authors show that complex acid lipids affect the precipitation of hydroxylapatite mineral in a physiological environment.

Recently some research has focused on the application of introducing exogenic molecules into cells by means of lipid complexes. These new lipids have an important clinical application for drug delivery and gene therapy. Since the lipids can be tailored to have different physical properties, the application may vary, Ashley et al 1996)[14] and Barber et al (1996)[15].

Different systems based on calcium phosphate granules and lipid carriers are described in literature, see for instance EP 0 429 419 which discloses a system where calcium phosphate, especially hydroxylapatite, is used as bone substitute material. In this case, use is made of a monoglyceride-based carrier, which may cause a drawback

in implant treatment since preliminary studies indicate that encapsulation may occur, which in turn can have a negative effect on implant integration.

Various systems for the release of pharmaceutical preparations containing bioceramic granules and lipid have also been described in literature, see for instance JP 2,631,890. As examples of different carriers for drugs and molecules that are to be released in bone tissue, mention can be made of collagen, lipids, polymers (for instance PLA/PGA and hyaluronic acid) and ceramics.

A large number of studies demonstrate that mineral deposition in cartilage that is being calcified is only found in vesicles containing phosphatidyl serine and alkaline phosphatase, and that the endocondral calcification process in the growth plate in the epiphysis can be mediated by these. Matrix vesicles and the negatively charged phospholipids therein seem to be involved in the initial formation of calcium hydroxylapatite crystals by way of the interaction between calcium and phosphate ions with phosphatidyl serine in the formation of phospholipid:calcium:phosphate ion complex, Boyan et al (1989)[16].

It is mainly the systemically blood calcium controlling hormones which in different ways control bone cells and, thus, keep the bone mass of the body in equilibrium. In recent years, many studies have been made which indicate that certain biopolymers of the polypeptide type produced by bone cells themselves and/or blood cells from bone marrow or in inflammation after, for instance, trauma, have an important and probably a more immediate importance for activating the individual cells in connection with the bone formation process.

Bone formation and bone resorption are connected to each other. Systemically and locally produced factors control

the processes. Many of the growth factors may have different effect on different cells. For instance, PTH and vitamin D can stimulate bone resorption and remodelling by means of the bone-forming cells, cf. Nijweide et al (1986)[17]. On the other hand, the bone-forming cells can be stimulated by TGF beta released of matrix during the bone resorption process, cf. Pfeilschifter et al (1990)[18].

The growth factors and cytokines that are produced by bone cells may have an autocrine or paracrine effect. Examples hereof are: TGF, IGF-I and IGF-II, Beta2 Microglobulin, PDGF and CSFs. Thrombocyte-derivated factors such as TGF, PDGF and EGF, but also interleukins, TNFs and Interferon gamma are factors of hematologic origin which have effect on the bone-forming cells. Growth factors which are stored in the bone matrix are the largest reservoir for growth factor activity. The factors stored are, as mentioned above, TGF, IGF-I and IGF-II, Beta2 Microglobulin, PDGF, but also FGF. Bone morphogenetic proteins, BMP, and osteogenine belong to the TGF family. BMP is usually combined with decalcified bone matrix and collagen, cf. Sampath and Reddi (1981)[19] and Saito et al (1994)[20]. Kuboki et al (1995)[21] have proved that BMP induces only bone better if the HA carrier consists of particles which are porous compared with non-porous.

In a newly published experimental study by Urist et al (1997)[22], different systems for administration of the growth factor BMP-2 and its effect on bone formation were investigated. The authors suggest that lipids extracted from bone can function well as a carrier of bone-stimulating peptides in the bone formation process.

Other molecules or ions which can bind strongly to crystal surfaces are, for example, bisphosphonates which can affect osteoblasts and thus dissolution of calcium phos-

phate compounds in the skeleton, cf. Ebrahimpour et al (1995)[23].

According to the invention, the preparation for restoring bone is a mixture of resorbable calcium phosphate granules and/or a carrier of a biopolymer or lipid type, where the lipid contains an esterified fatty acid selected from the group consisting of triglycerides, diglycerides or phospholipids or combinations thereof. The invention aims at overcoming the difficulties described above and constituting a preparation which easily and in a repetitive manner can be used in connection with bone implants. More specifically, the inventive material is intended to withstand dilution and transporting away from the area of application. Such a mixture can be given the "correct" consistency depending on the type of application, it can be made, for example, mouldable, and it is easy to handle, control and apply.

A desirable weight ratio between calcium phosphate and phospholipid is in the order of 70:15 to 60:40. A desirable weight ratio between phospholipid and water or other water-based liquids is in the order of 1:2 to 10:1, preferably 3:2 to 4:1.

With reference to the water-based liquid that is used to make the preparation mouldable, pure water, an isotonic saline solution or a pharmaceutically acceptable solution are preferred. In some cases when the preparation is being produced in situ, body fluids including blood can be used.

The invention will now be described in more detail in connection with some applications of bone implants where the surrounding bone tissue need to be reinforced and/or built-up,

Fig. 1 showing a case where the bone forms a far too loose, load-carrying network,

Fig. 2 showing a case where the lateral bone volume is insufficient,

Fig. 3 showing a case having angular and/or too narrow bone ridges,

Fig. 4 showing a case where the vertical bone height is insufficient, and

Fig. 5 being a picture of a preparation applied in rabbit bone.

As mentioned by way of introduction, the preparation for restoring bone consists of a mixture of resorbable calcium phosphate granules and a carrier of a biopolymer or lipid type. To be applied in connection with a bone implant and be kept in the area of application, it is important for the mixture to be mouldable and to have the correct consistency. If the particles are transported away from the area of application, they could cause irritation or complications in other positions in the body.

The calcium phosphate granules should have a Ca/P ratio of between 1 and 2. The granules should have an average diameter of 0.05 - 5 mm and a micro/macro porosity of 0-80%.

In a study made by Neo et al (1992)[24], the interface between bioactive ceramics and bone was studied by using scanning and transmission electron microscopy. Calcium phosphate granules having an average diameter of 0.1 to 0.3 mm were studied and characterised in respect of resorbability. After 8 weeks, the non-resorbable granules were connected with bone by a thin Ca-P-rich layer con-

sisting of fine apatite crystals, however, different from those in bone in respect of shape, size and orientation. The resorbable granules, however, had direct contact with the bone. The surface of the granules was coarser owing to degradation, and analyses demonstrated that bone grew into the smallest surface irregularities. In another study made by Kitsugi et al[25], four types of calcium phosphate ceramics were compared. The Ca/P ratio was in this case 1, 1.5 and 1.66 and the size of the particles (granules) varied between 0.15 and 0.3 mm. Observations made by transmission electron microscopy showed that the Ca/P ratio did not affect the connection and contact between the particles and the surrounding bone.

According to the invention it is necessary to have a carrier for the resorbable calcium phosphate granules, which may consist of a biopolymer or a lipid containing esters of fatty acids, such a triglyceride, diglyceride, or phospholipids or combinations thereof, for instance some of the lipids described in WO 95/34287.

Preferably, the calcium phosphate granules are distributed in a lamellar, liquid crystalline phase which contains at least one phospholipid and forms either in the body or earlier.

Example 1

The following Example describes a test for the handleability of a HA granule/lipid mixture, a phospholipid, (Epikuron 200 supplied by Lucas Mayer) being mixed with HA granules (in this case Apaceram by Pentax) and ethanol, series A samples 1-8. These samples have then been freeze-dried to a constant weight. After freeze-drying, the samples have a composition which is evident from the Table below.

In series B, samples 9-17 have been mixed according to the Table below, whereupon the mouldability has been assessed. The samples were made by 0.9% by weight NaCl in water (physiological salt solution) being weighed and mixed with phospholipid (PC), whereupon hydroxyapatite granules were added. All samples in this series contained 70% by weight of HA and the amount of granules has been kept constant whereas the ratio of phospholipid to water has been varied. The samples that contain only two components PC and granules, as well as water and granules, did not have a satisfactory handleability.

Series A, samples 1-8

SAMPLE No.	PC %	HA %	CONSISTENCY
1	10.1	89.9	crumbly
2	15.1	84.9	crumbly
3	20.1	79.9	crumbly
4	25.0	75.0	slightly mouldable
5	30.1	69.9	mouldable
6	35.1	64.9	mouldable
7	40.0	60.0	mouldable
8	45.0	55.0	mouldable

Series B, samples 9-17

SAMPLE No.	PC %	0.9% NACL ISG	HA %	CONSISTENCY
9	3.2	27.0	69.9	crumbly
10	6.0	24.0	70.0	crumbly
11	9.2	20.9	69.9	crumbly, slightly mouldable
12	12.0	18.1	69.9	crumbly, slightly mouldable
13	15.0	15.2	69.9	slightly mouldable
14	18.0	12.0	70.0	mouldable
15	21.1	9.1	69.8	mouldable
16	24.1	6.1	69.8	mouldable
17	27.0	3.0	70.0	crumbly, slightly mouldable

The weight ratio between the calcium phosphate component and the lipid and the admixture of water are determined by the requirement that the preparation should be easily handleable and mouldable. Preferably, the weight ratio between calcium phosphate and phospholipid should be within the range 70:15 to 60:40. The weight ratio of phospholipid to water or some other water-based liquid should be in the range 1:2 to 10:1, preferably 3:2 to 4:1.

Example 2

Mouldable preparations were produced by mixing 0.21 g phospholipid (1,2-dioleyl-sn-glycero-3-phosphocholine, Avanti Polar Lipids, Inc.) with 0.12 g 0.9% physiological salt solution. After one hour, 0.71 g hydroxyapatite granules (OsteoGen® (HA Resorb)®, Impladent Ltd.) was added. The preparation was mixed to a mouldable consistency and was easy to pack in an applicator.

The preparation was evaluated in respect of handleability and applicability in a defect model where circular defects having a diameter of 4 mm had been created in the lower part of the leg (tibia) on adult New Zealand White rabbits. The evaluation shows that the preparation was handleable and easy to apply in the defect area with a modified syringe. The preparation was kept together and was not affected by the relatively strong flow of blood from the area of the wound. Fig. 5 is a picture of the applied preparation inserted in the rabbit bone. An evaluation is now made in respect of the amount of newly formed bone (histomorphometrically) in the defect area, and the result will be compared in pairs with an untreated defect produced in an identical manner.

Instead of a lipid of the type described above, the carrier can consist of a biopolymer, a proteoglycan, a glycoseaminoglycan, for instance hyaluronic acid. Hyaluronic acid is an anionic polysaccharide, composed of repetitive disaccharide units of beta-1-4-glucoronate-beta-1-3-N--acetyl-glucoseamine and is part of the extracellular matrix. Hyaluronic acid serves as lubricant in joints, is present in large quantities in connective tissue and is present in abundance in the eye. In a study investigating whether phagocytable particles of hydroxyapatite have a detrimental effect on bone formation, sodium hyaluronic acid has been used as a carrier solution for hydroxyapatite, cf. Wang J-S et al (1994)[26].

The following formulation of hyaluronic acid and hydroxyapatite can be used as bone substitute material according to the invention. A freeze-dried mixture of sodium hyaluronic acid (Healon®) and hydroxyapatite (65:35%w/w) swells in the presence of water and thus is easy to form and handle. The freeze-dried mixture of sodium hyaluronic acid and hydroxyapatite is easily packed in an applicator and/or a modified syringe, which is rehydrated with

water, an aqueous solution or body fluid close to the application so as to form a mouldable hydroxyapatite formulation for restoring bone.

The bone restoring material according to the invention or the granules themselves can advantageously be combined with a cell-stimulating substance which is known per se, for instance growth factors such as BMP and relating to the TGF beta family. Bone-stimulating substances and molecules transmit signals and affect cells and cellular activities in bone. Proteins and polypeptides are examples of substances which have been found to have a bone-stimulating effect in different ways, mainly locally. In addition to the fact that the preparation can be mixed with a bone implant from the patient himself, calcium phosphates granules can be added, containing bone-stimulating substances or parts thereof.

Depending on the properties of the bone-inducing or tissue-promoting factors, some of them exist in an active and an inactive form, respectively, and need be combined with different types of carrier to induce bone and cartilage *in vivo*. First this was explained by the fact that the growth factor diffused out too fast and was not kept in place sufficiently long for an effect to be achieved. Later studies have proved that the carrier also serves as support and substrate for cells to adhere to and diffuse on since bone formation can occur only on a surface or substrate, cf. Kuboki et al (1995)[21]. Common examples of a carrier for BMP are decalcified bone matrix and collagen, cf. Sampath and Reddi (1981)[19] and Saito et al (1994)[20]. Kuboki et al (1995)[21] have demonstrated that BMP induces only bone if the HA carrier consists of particles that are porous. Tsuruga et al (1997)[27] present theories about cell differentiation and bone formation being strongly dependent on the carrier in its capacity as substrate surface and microenvironment. According to the invention

it is thus suggested that the mouldable calcium phosphate granule-lipid mixture is allowed to constitute a carrier for, for example, growth factors.

Some examples of situations in which the invention can be applied will be illustrated below with reference to Figs 1-4:

Fig. 1

A. After boring (and prethreading) of the bone, B. the preparation is applied in the produced bore by means of a syringe or an inserting appliance. The preparation is pressed against the walls of the cavity and, owing to the bone architecture consisting of no network at all or a loose network, the penetration of the preparation peripherally outwards in the tissue is made possible. C. A helical bone implant (fixture) is installed according to a standard procedure and, after integration, the bone round the fixture has been remodelled and assumed a more lamellar structural appearance and thus is also capable of absorbing loads in a more advantageous manner.

Fig. 2

A. After boring (and prethreading), B. the preparation applied in the produced bore by means of, for instance, a syringe or a similar inserting appliance. The preparation is applied in the defect and, owing to the consistency of the preparation, the granules remain in the application area and thus enable new formation of bone in the defect area. C. The fixture can be installed according to a standard procedure directly by bicortical fixing, D. but also after a short or long period of integration when the

bone in the area has been converted and assumed a more lamellar structural and cortical appearance.

Fig. 3

A. After boring (and prethreading), B1. the preparation is applied before the fixture is installed or B2. after the fixture has been installed in the case of unsatisfactory vertical and horizontal bone volume, for instance angular defects and/or too narrow bone ridges. These two situations are examples of situations where part of the fixture initially does not have a satisfactory contact with the surrounding bone tissue. C. After integrating, the healing process has produced the normal bone architecture in the area.

Fig. 4

After toothlessness in the upper jaw, the sinus has in many cases expanded while at the same time the bone ridge has been resorbed. This means that the vertical height that is required for the anchoring of fixtures is insufficient.

Alternative I A. After boring (and prethreading), B. the preparation is applied by means of a modified syringe or some other appliance under the mucous membrane of the sinus. C. The fixture is installed and after unaffected integrating the preparation results in new bone forming in connection with and in contact with the fixture.

Alternative II In a sinus lift, the preparation can also be applied laterally, i.e. communication with the sinus occurs by way of a laterally produced defect, whereupon the mucous membrane of the sinus is lifted and

parts of the bottom of the sinus can be filled with the preparation.

Fig. 5

The picture illustrates a preparation according to Example 2 above applied in a rabbit bone, as described above.

CLAIMS

1. A preparation for restoring bone in the body of humans or animals in connection with an existing structure, a bone implant or some other prosthetic construction, the preparation being intended to be applied in the position in connection with, for instance, a bone implant or some other prosthetic construction where there is a lack of sufficient bone volume, or where the quality of the bone is too poor, or to allow a load-carrying function, c h a r a c t e r i s e d in that the preparation consists of an easily handleable, controllable and decomposable carrier preparation of calcium phosphate granules or a biological organic component of a biopolymer and/or lipid type.

2. A preparation as claimed in claim 1, c h a r a c t e r i s e d in that the preparation has a mouldable consistency.

3. A preparation as claimed in claim 2, c h a r a c t e r i s e d in that the preparation has been made mouldable by admixing water or some other water-based liquid, such as body fluid.

4. A preparation as claimed in claim 2, c h a r a c t e r i s e d in that the lipid consists of a mixture of esterified glycerol and phospholipid.

5. A preparation as claimed in claim 4, c h a r a c t e r i s e d in that the esterified glycerol consists of di- and triglyceride.

6. A preparation as claimed in claim 4, c h a r a c t e r i s e d in that the esterified glycerol is a diester.

7. A preparation as claimed in claim 4, c h a r a c - t e r i s e d in that the esterified glycerol is a triester.

8. A preparation as claimed in claim 2, c h a r a c - t e r i s e d in that the lipid consists of a mixture of phospholipids.

9. A preparation as claimed in claim 8, c h a r a c - t e r i s e d in that the phospholipid is a sphingomyelin.

10. A preparation as claimed in claim 8, c h a r a c - t e r i s e d in that the phospholipid is a phosphatidyl choline.

11. A preparation as claimed in claim 2, c h a r a c - t e r i s e d in that the lipid is prepared from a vegetable oil or egg yolk.

12. A preparation as claimed in any one of the preceding claims, c h a r a c t e r i s e d in that the lipid consists of at least one phospholipid and water or some other water-based liquid as carrier.

13. A preparation as claimed in claim 12, c h a r a c - t e r i s e d in that the lipid is in a lamellar floating crystalline phase.

14. A preparation as claimed in claim 12, c h a r a c - t e r i s e d in that the weight ratio between lipid and water or some other water-based liquid is in the order of 1:2 to 10:1, preferably 3:2 to 4:1.

15. A preparation as claimed in claim 2, c h a r a c - t e r i s e d in that the biopolymer contains a glycose-aminoglycan, for example hyaluronic acid.

16. A preparation as claimed in claim 15, c h a r a c - t e r i s e d in that it consists of a free-flowing mixture of sodium hyaluronic acid and calcium phosphate granules which can be packed and then rehydrated in connection with use.

17. A preparation as claimed in claim 1, c h a r a c - t e r i s e d in that the calcium phosphate granules have a Ca/P ratio which is between 1 and 2.

18. A preparation as claimed in claim 17, c h a r a c - t e r i s e d in that the calcium phosphate contains hydroxyapatite of the form $Ca_{10}(PO_4)_6(OH)_2$.

19. A preparation as claimed in claim 17, c h a r a c - t e r i s e d in that the calcium phosphate contains dicalcium phosphate dihydrate, octacalcium phosphate, tricalcium phosphate and/or hydroxyapatite.

20. A preparation as claimed in claim 17, c h a r a c - t e r i s e d in that the calcium phosphate contains magnesium, fluorine or carbonate ions.

21. A preparation as claimed in claim 17, c h a r a c - t e r i s e d in that the calcium phosphate granules have a diameter in the order of 0.05 mm to 5 mm.

22. A preparation as claimed in claim 17, c h a r a c - t e r i s e d in that the calcium phosphate granules have a porosity of 0-80%.

23. A preparation as claimed in any one of the preceding claims, c h a r a c t e r i s e d in that the weight ratio between the calcium phosphate granules and the lipid is in the order of 70:15 to 60:40.

24. A preparation as claimed in any one of the preceding claims, characterised in that it contains tissue-promoting factors and/or factors which inhibit decomposition of tissue, for example a growth factor, such as BMP and TGF beta or parts thereof.

25. A preparation as claimed in claims 3, 16 and 24, characterised in that the tissue-promoting factor is added wholly or partially.

26. A method for restoring bone in the body of humans or animals in connection with an existing structure, a bone implant or some other prosthetic construction, characterised by applying an easily handleable and controllable preparation of resorbable calcium phosphate granules and a biological organic carrier of a biopolymer or lipid type in the position in the body in connection with, for example, a bone implant or some other prosthetic construction where there is a lack of sufficient bone volume, or where the quality of the bone is too poor to allow a load carrying function.

27. A method as claimed in claim 26, characterised by applying the preparation in a produced or existing cavity or defect in the bone by means of a syringe or planing appliance.

28. A method as claimed in claim 26, characterised by applying the preparation in a cavity produced for a bone implant.

29. A method as claimed in claim 26, characterised by applying the preparation in a bone defect, for example an angular defect in connection with an already installed bone implant or a cavity produced for a bone implant.

30. A method as claimed in claim 26, c h a r a c t e r - i s e d by applying the preparation on the bone under the mucous membrane of the sinus for the purpose of increasing the vertical height of the bone ridge.

Fig. 1

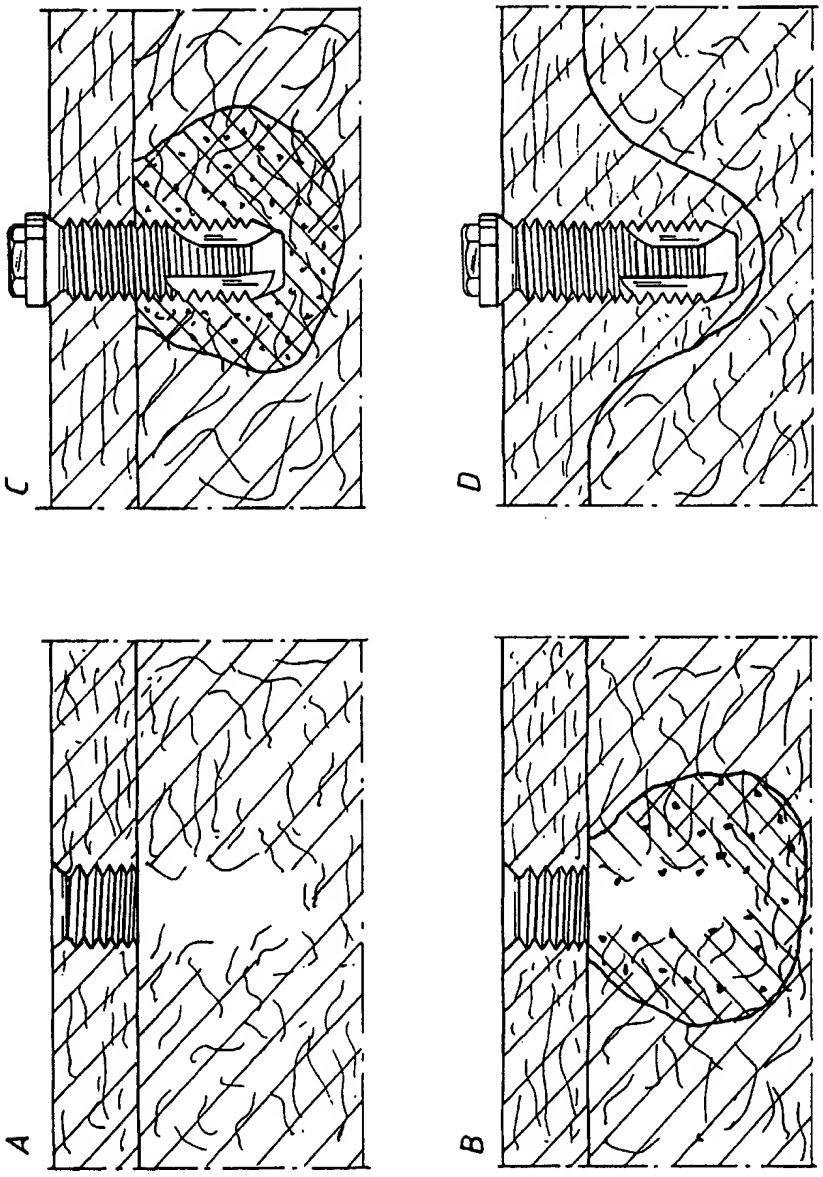


Fig 2

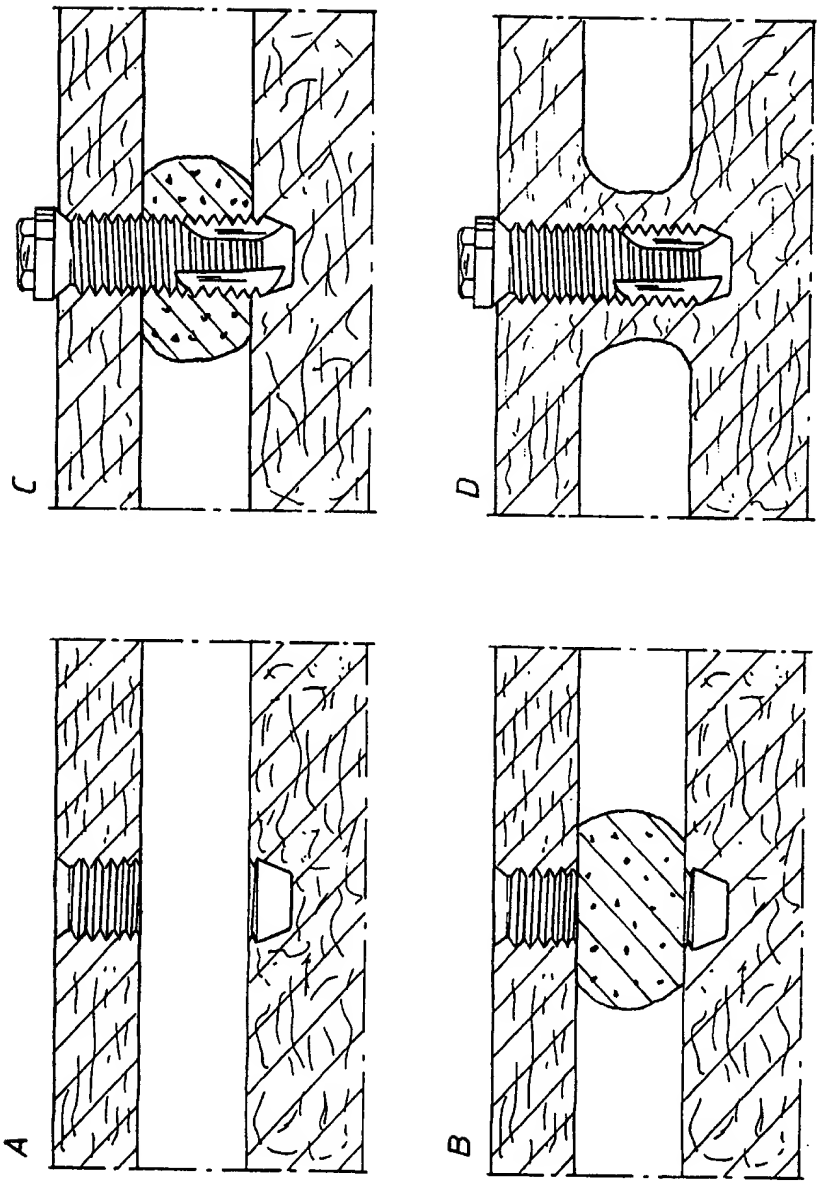


Fig. 3

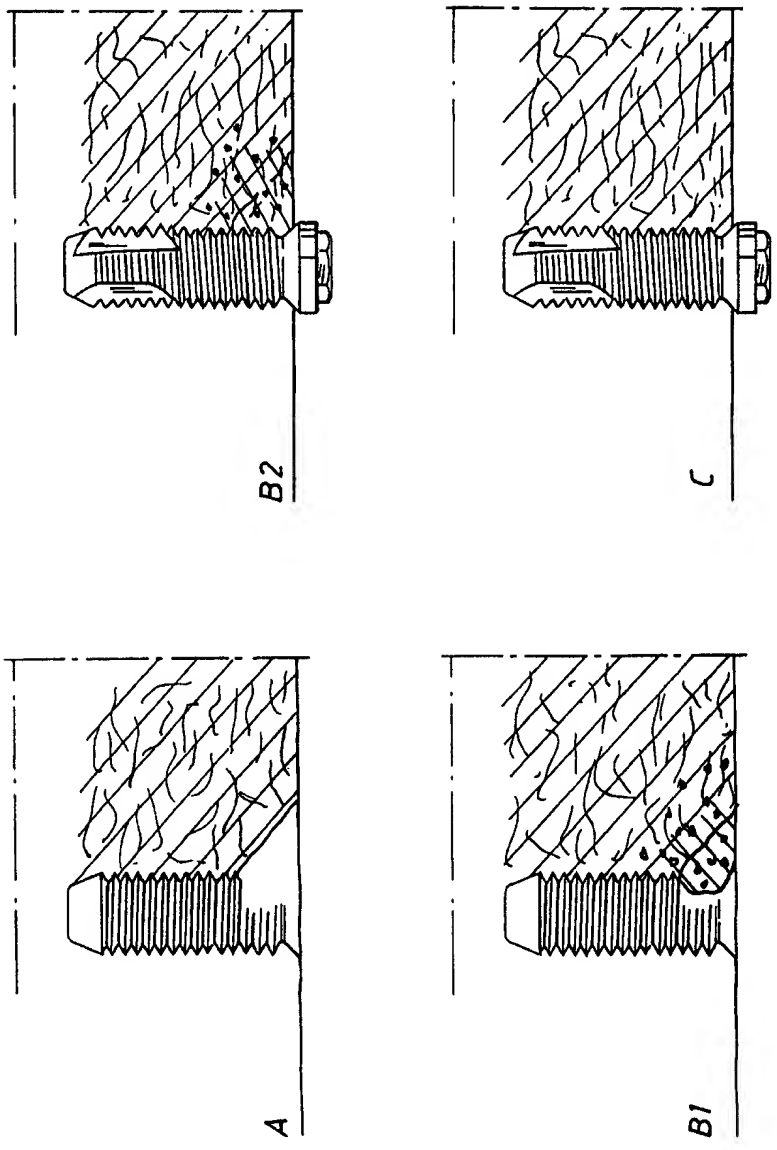


Fig 4

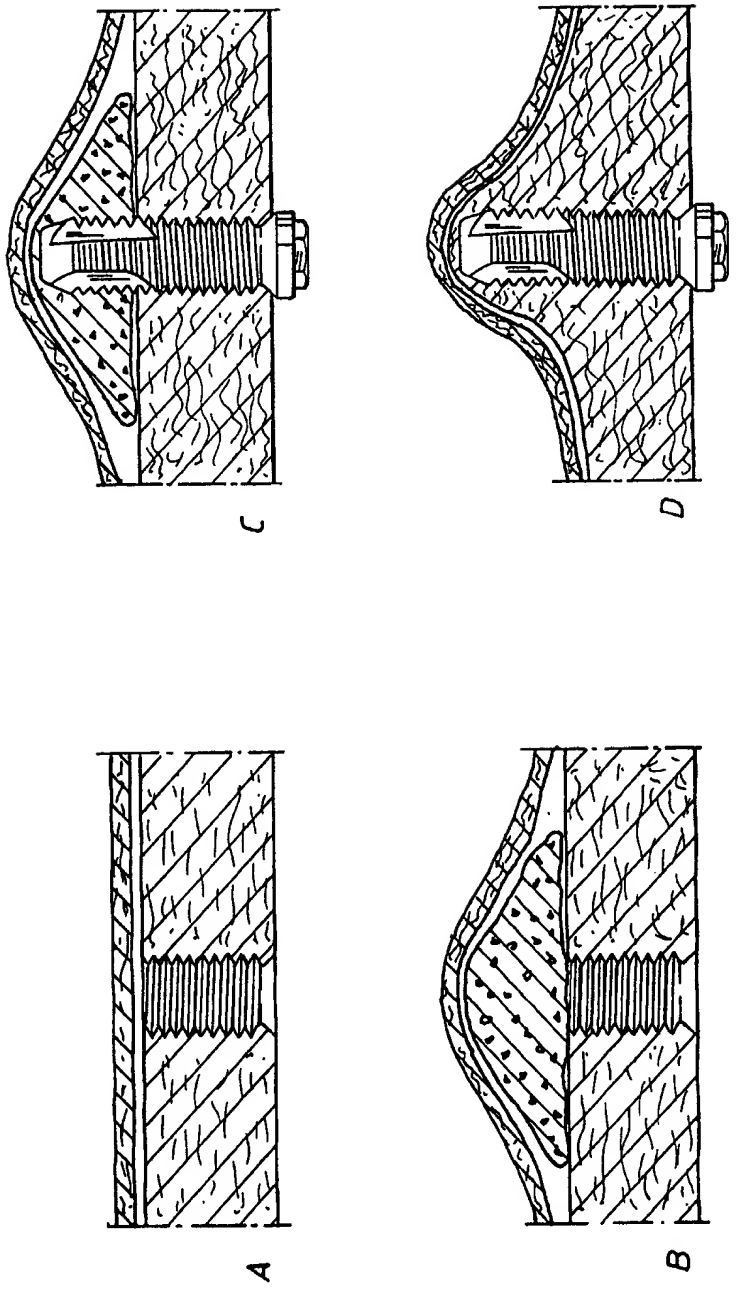
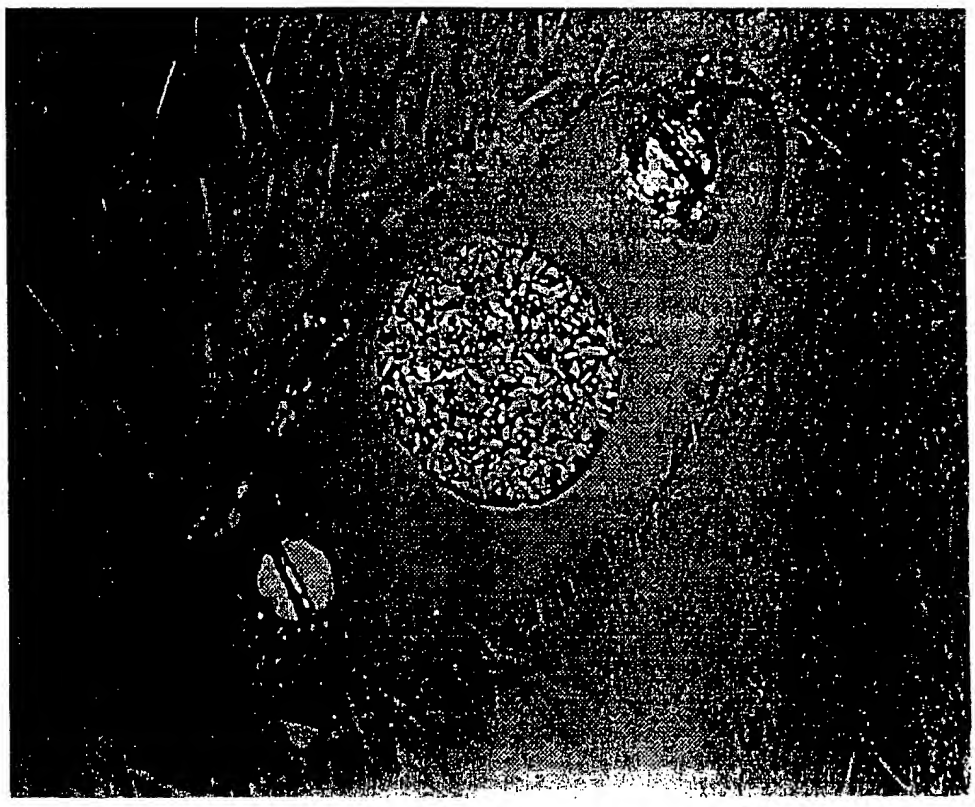


Fig. 5



INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/01231

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61L 27/00, A61F 2/28
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61L, A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4192021 A (HEINRICH DEIBIG ET AL), 11 March 1980 (11.03.80), claims, abstract --	1-25
X	US 5338772 A (HANS-JÖRG BAUER ET AL), 16 August 1994 (16.08.94), claims, abstract --	1-25
A	US 5092888 A (OSAMU IWAMOTO ET AL), 3 March 1992 (03.03.92), claims, abstract --	1-25
A	WO 9745147 A1 (ONTARIO INC.), 4 December 1997 (04.12.97), claims, abstract --	1-25

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 October 1999	09 -11- 1999
Name and mailing address of the ISA/ Swedish Patent Offic Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Jack Hedlund/ELY Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/01231

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5769897 A (ANTON HÄRLE), 23 June 1998 (23.06.98), claims, abstract ---	1-25
A	SE 464912 B (BIOAPATITE AB), 1 July 1991 (01.07.91), claims, abstract --- --------	1-25

INTERNATIONAL SEARCH REPORT

International application No.
SE99/01231

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 26-30
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1 (iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/09/99

International application No.
PCT/SE 99/01231

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CA 2252860 A	04/12/97
		EP 0906128 A	07/04/99
US 5769897 A	23/06/98	NONE	
SE 464912 B	01/07/91	SE 8903538 A	26/04/91